REMARKS

Status of the claims

Claims 1-30 and 32-39 remain in prosecution. Claims 1, 4, 8-11, 14, 15, 20, 25, 26, and 32 are amended herein without any intent of disclaiming equivalents thereof. Claims 7, 13, 21, 24, 28-31, and 33-39 are cancelled herein without prejudice to Applicant's right to pursue their subject matter in this application or in related applications. New claims 40 and 41 are added herein. Thus, upon entry of this amendment, claims 1-6, 8-12, 14-20, 22, 23, 25-27, 32, 40, and 41 will be pending and presented for examination.

Amendments to the drawings

The drawings stand objected to because two Figures 2a were submitted and because reference character S400 in original Figure 4 is not mentioned in the description.

Applicant submits herewith two sheets of replacement figures to replace sheet 3/7 (Figures 2b and 2a) and sheet 5/7 (Figure 4) as originally filed, labeled "Replacement Sheet" in accordance with 37 CFR §1.121. In Replacement Sheet 3/7, "Figure 2a" has been relabeled "Figure 2c." In Replacement Sheet 5/7, reference character S400 has been deleted from Figure 4. The amendments to the drawings introduce no new matter.

Applicant submits that the figures as amended overcome the objection and respectfully request reconsideration and withdrawal of the objection.

Amendments to the claims

Claims 1, 4, 9, 20, and 32 are amended as described below. Claims 8-11, 14, 15, 25, and 26 have been amended to remove dependencies from canceled claims.

The amendments to the claims introduce no new matter.

Rejections under 35 U.S.C. §112, second paragraph

Claims 4 and 9 stand rejected under 35 USC §112 as having a narrow range within a broad range in the same claim. Claim 4 has been amended to recite a single range. Claim 9 has been amended to recite the proper dependency in view of the cancelled claim, to clearly recite which parameter is selected and further to recite a single range. Applicant submits that amended claims 4 and 9 overcome the rejection and respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. §101

Claims 28, 29 and 39 stand rejected under 35 USC §101 as allegedly directed toward non-statutory subject matter because the carrier may be either an optical or electrical carrier. Claim 30 stands rejected under 35 USC §101 directed toward non-statutory subject matter as a computer program.

Claims 1-4, 7-9, 13-17, 19-27, and 33-38 stand rejected under 35 USC §101 as directed toward non-statutory subject matter.

The cancellation of claims 7, 13, 21, 24, 28-30, and 33-39 renders their rejection moot.

Applicant traverses the rejection to the extent it is maintained over independent claims 1 and 20, as amended. Claims 1 and 20 are drawn to methods for using biological parameters (e.g., biological markers) to generate likelihood ratio data for determining the likelihood of an at-risk pregnancy. Specifically, the assayed levels of physical substances—biological parameters—are measured in samples from a pregnant woman, and the measured levels are then converted

into likelihood ratio data from which the probability of an affected fetus can be determined. Thus, at least one material transformation occurs: converting a tangible amount of a biological parameter into likelihood ratio data. Moreover, even if the Examiner considers the measured biological parameter levels to be non-physical information, this information is still transformed into a materially different thing in the form of risk likelihood data, such as a risk assessment table. Applicant therefore submits that amended claims 1 and 20 are directed to statutory subject matter, as are claims 2-4, 8-9, 14-17, 19, 22, 23, 25-27, 33-38, 40, and 41 which ultimately depend from claims 1 and 20. Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-11, 13-26, 28-30 and 32-39 stand rejected as unpatentable over Davies (EP0800085). Claims 4 and 9 stand rejected under 35 USC §103 as upatentable over Davies. Claims 7, 13, 21, 24, 33-39 are herein cancelled.

Davies (EP0800085) discloses a method for prenatal screening for Down's Syndrome. In the method disclosed by Davies the level of hCG or the free alpha or beta subunit thereof is measured at a first and second week and the level at the second week is divided by the level at the first week to form a normalized value. This normalized value is compared to populations of women with and without Down's Syndrome affected pregnancies and deviations determined.

That is, Davies measures two values at two time points during a pregnancy uses the two values to form a normalization value which is compared to populations of normal and Down's Syndrome pregnancies.

In contrast, claim 1 of the instant application recites:

1. (currently amended) A method of determining a likelihood of a fetus carried by a pregnant mother having a chromosomal abnormality~~,~~ using a first biological~~,~~ parameter ~~being~~ which is suitable for screening said fetus for said chromosomal abnormality, the method comprising:

receiving first data from a first stage of pregnancy of said mother, said first data comprising data representing a first value of said first biological parameter and data re resenting a first value of a second biological parameter, wherein said second biological parameter is suitable for screening said fetus for said chromosomal abnornia1ity;

receiving second data from a second, later stage of said pregnancy, said second data comprising data representing a second value of said first biological parameter and data representing a second value of said second biological parameter;

determining a multiple of median value for each of said values in said first and second data by dividing each of said values in said first and second data by corresponding predicted median value;

forming a feature vector y using said multiple of median values;

determining a probability of an unaffected pregnancy given feature vector y;

determining a probability of an affected pregnancy given feature vector y, and

determining likelihood ratio data from said first and second data by calculating a ratio of said probability of an unaffected pregnancy to said probability of an affected pregnancy, said likelihood ratio data representing the likelihood of said fetus having a chromosomal abnormality.

Similarly, claim 20 recites:

20. (currently amended) A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's Syndrome, the method comprising the steps of:

measuring ~~at least one~~ a first screening marker level from one of a first and second stage of pregnancy by assaying a sample obtained from the pregnant woman at said first or second stage of pregnancy for at least one biochemical screening marker;

measuring a level of the same said ~~at least one~~ first screening marker at the other of said first and second stage of pregnancy by assaying a sample

obtained from the pregnant woman at said other stage of pregnancy for said at least one biochemical screening marker;

measuring a second screening marker level from one of said first and second stage of pregnancy by assaying a sample obtained from, the pregnant woman at said first or second stage of pregnancy for said a second biochemical screening marker;

measuring a level of said second screening marker at the other of said first and second stage of pregnancy by assaying a sample obtained from the pregnant woman at said other stage of pregnancy for said second biochemical screening marker; and

determining a quantitative estimate of the risk of Down's Syndrome using the measured screening marker levels from both the first and second stages of pregnancy by expressing each of said measured screening marker levels as a logarithm of a multiple median value by dividing each of said measured screening marker levels by a corresponding predicted median value to form a feature vector y; and

determining said quantitative estimate from a ratio of a probability of an unaffected pregnancy given feature vector y and a probability of an affected pregnancy in which said fetus has said abnormality given feature vector y.

Claim 32 also recites:

32. (Currently amended) A computer system for providing risk data representing a likelihood of a fetus carried by a pregnant mother having a chromosomal abnormality~~,~~ using a first biological parameter being suitable for screening said fetus for said chromosomal abnormality, the computer system comprising:

a data store operable to store data to be processed;

an instruction store storing processor implementable instructions; and

a processor coupled to said data store and to said instruction store and configured to load and implement said stored instructions, said instructions comprising instructions for controlling the processor to:

input first data from a first stage of pregnancy of said mother, said first data comprising data representing a first value of said first biological parameter and data representing a first value of a second biological parameter, wherein said second biological parameter is suitable for screening said fetus for said chromosomal abnormality;

input second data from a second, later stage of said pregnancy, said second data comprising data representing a second value of said first biological parameter and data representing a second value of a second biological parameter;

determine said risk data from said fast and second data by expressing each of said first and second data as a logarithm of a multiple median value by dividing each of said first and second data by a corresponding predicted median value to form a feature vector y;

determining said likelihood ratio data from a ratio of a probability of an unaffected pregnancy given feature vector y and a probability of an affected pregnancy in which said fetus has said abnormality given feature vector y; and

output said determined risk data.

Thus, in each of the independent claims, two biological parameters are measured at two points in time and feature vectors constructed using the median values of the parameters and determining a ratio of the two feature vectors to determine likelihood ratio data. That is, in the present invention, two different markers are each measured at two stages. The values of each marker are compared with a predicted value at both stages to determine four multiple of median values (one for each marker at each stage). In other words, as set out on page 18, the first stage is to compare an individual woman's marker results with appropriate reference values to correct for changes in marker levels due to gestational age. This produces standardized values (see also page 22) which are comparable across all gestational ages.

The standardized parameters form a feature vector y which is used to determine the probability of an unaffected pregnancy given this feature vector and to determine the probability of an affected pregnancy given this feature vector. Details of how this may be achieved are set out from page 22 onwards. As explained on page 16, the feature vector can be thought of as defining a point in multi-dimensional space in which two surfaces are defined; one for affected pregnancies and one for unaffected pregnancies. At this point in space, both the unaffected pregnancies surface and the affected pregnancies surface have the corresponding height

representing a probability of that combination of features being associated with an unaffected and an affected pregnancy respectively. The ratio of these two heights is in effect, the likelihood ratio.

Davies, which is directed to a method for prenatal screening for fetal abnormalities, also recognizes the problem of the influence of subject variation (page 2, line 30). However, the solution used in Davies differs from that of the present invention. In Davies, as described on page 2, lines 31 to 35, determination of the concentration of a marker are made at two stages (stages A and B) in pregnancy. These two values are compared to produce a normalized concentration C (lines 47-49) which may be achieved, e.g. by simply dividing the value at stage B with the value at stage A (page 3, line 35). This process may be repeated for another marker (page 4, line 5). The normalized concentration C is then compared with a normalized value for the whole population, to derive the multiple of the median MoM (page 4, line 20).

In other words, the solution in Davies is to use one measured value to "normalize" another and then compare the normalized measured value with the predicted normalized value to derive a MoM. Thus, comparison with a predicted value occurs at a different step in Davies. There is no teaching in Davies of comparing <u>each</u> measured value with a predicted median value and no suggestion that would lead a skilled man to modify Davies to arrive at this feature.

In Davies, since the two measured values are combined to form the normalized value C, the marker used must discriminate clearly from the normal (i.e. above 50%) at one stage but not from the normal (i.e. below 20%) at the other stage. In contrast, in the present invention, the "standardized" measured values are individually included in the feature vector and thus the discriminatory information from each measurement is retained. The measurements may be considered to be symmetrically included in the calculation of the likelihood ratio. Accordingly,

the methodology of the present invention is applicable to markers which discriminate either at both stages of pregnancy or only at one stage. For example, PAPP-A is discriminatory in both the first and second stages and thus it is more effective to use the methodology of the present invention to incorporate both measurements of PAPP-A than the methodology of Davies in which the two measurements of PAPP-A are combined into a single value C.

Similarly, claims 12 and 27 stand rejected 35 USC §103 as unpatentable over Davies and further in view of Benattar *et al.*

Davies is described above. Benattar *et al.* in "Efficiency of Ultrasound and Biochemical Markets for Down's Syndrome Risk Screening" discloses using ultrasound to measure fetal nuchal transluncency in conjunction with α-fetoprotein, hCG and free β-hCG measurements. Benattar *et al.* also does not teach or suggest calculating feature vectors using median values of the parameters and determining a ratio of the feature vectors to determine likelihood ratio data. This Benattar *et al* does not make up for the deficiencies of Davies. In addition Applicant submits that claims 12 and 27 are now allowable as depending from an allowable base claim.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance and therefore request early favorable action by the Examiner.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Respectfully submitted,

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